IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CEPHALON, INC. and CIMA LABS, INC.,	)	
Plaintiffs,	)	C.A. No. 08-330-SLR
v.	)	
WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC., and WATSON PHARMA, INC.,	)	PUBLIC VERSION
Defendants.	)	
CEPHALON, INC.,	)	
Plaintiff,	)	C.A. No. 09-724-SLR
v.	)	
WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC., and WATSON PHARMA, INC.,	)	PUBLIC VERSION
Defendants.	)	

CORRECTED DEFENDANTS' REPLY POST-TRIAL BRIEF

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INTRODUCTION

Defendants submit this brief in further support of their arguments that the asserted claims of U.S. Patent Nos. 6,264,981 ("the '981 patent"), 6,200,604 ("the '604 patent"), and 6,974,590 ("the '590 patent") are invalid. Plaintiffs' validity arguments fail at least because:

- Plaintiffs improperly rely on subjective testimony from the inventors to distinguish the key prior art from the asserted patent claims, effectively importing limitations and motivations from the inventors' own work that are not found within the objective reach of the construed claims.
- Plaintiffs wrongly apply the law on "teaching away" to argue that key prior art would not be combined by incorrectly focusing on preferences or differences in a reference that do not discourage, and are not inconsistent with, such combination.
- Plaintiffs do not meet their burden of presenting relevant, objective evidence of secondary indicia of nonobviousness sufficient to rebut Defendants' *prima facie* obviousness cases.

Defendants present clear and convincing evidence that the asserted claims of the '981, '604, and '590 patents are invalid.

ARGUMENT

I. PLAINTIFFS' NONOBVIOUSNESS ANALYSIS IS DIRECTLY AT ODDS WITH CONTROLLING LAW.

To rebut Defendants' obviousness case, Plaintiffs engage in an analysis that is inconsistent with Supreme Court precedent. Plaintiffs perform a *subjective* analysis, focusing on the testimony of inventors Dr. Zhang and Dr. Khankari. Through this lens, Plaintiffs narrowly characterize the asserted claims, limit the scope and content of the prior art, and use the inventors' personal motivations to argue that the objective person of ordinary skill in the art would have no motivation to combine the prior art references. This approach is legally improper. In an obviousness determination, "*neither the particular motivation nor the avowed purpose of the patentee controls.* What matters is the objective reach of the claim. If the claim

extends to what is obvious, it is invalid under [35 U.S.C.] § 103." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-20 (2007) (emphasis added).

A. Defendants Have Properly Articulated The Objective Reach Of The Claims, While Plaintiffs Have Focused On Subjective Testimony Of The Inventors.

Defendants properly ground their *prima facie* case of obviousness on the objective reach of the claims and the perspective of the objective skilled artisan. D.I. 245 (08-330-SLR) at 15-29, 38-50; *see KSR*, 550 U.S. at 420. In contrast, Plaintiffs rely heavily on subjective inventor testimony regarding their motivations toward solving alleged problems, the solutions to which Plaintiffs now allege are claimed in the patents at issue. *See, e.g.*, D.I. 251 (08-330-SLR) at 7-8, 13, 19-22, 49-52; Tr. 1420:20-24, 1423:2-1424:12, 1427:18-1430:2, 1430:23-1432:22, 1455:12-16, 1458:20-1459:2 (Byrn direct). By doing so, Plaintiffs fail to restrict their analyses to the objective reach of the claims, as they must. *KSR*, 550 U.S. at 419-20. For example, regarding the '981 patent, Cephalon contends that "Dr. Zhang's invention was not directed to simply improving a drug's solubility, but rather Dr. Zhang invented formulations to improve and control a drug's dissolution, solubility, absorption, and stability." D.I. 251 (08-330-SLR) at 8 (citations omitted); *see also id.* at 7, 22. And regarding the Orange Book patents, Plaintiffs argue: "[A]s the Khankari patents detail, the problem addressed was increasing the onset of action and avoiding first pass effect more so than earlier transmucosal formulations." *Id.* at 49 (citations omitted). Such descriptions are inconsistent with the objective reach of the asserted claims, which do not encompass all of these limitations. D.I. 245 (08-330-SLR) at 15-19, 39-41.

This Court's obviousness inquiry must be objectively based. *See KSR*, 550 U.S. at 420 ("The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art . . . ."); *see also Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("[T]his inquiry, as a matter of

law, is independent of the motivations that led the inventors to the claimed invention."). The Supreme Court in *KSR* identified the lower court's errors, particularly the court's improper, subjective analysis:

> The first error of the Court of Appeals in this case was to foreclose this reasoning by holding that courts and patent examiners should look only to the problem the patentee was trying to solve . . . . The second error of the Court of Appeals lay in its assumption that a person of ordinary skill attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem.

550 U.S. at 420 (citation omitted). Here, Plaintiffs engage in the same subjective analysis that the Supreme Court rejected in *KSR*.

B. Plaintiffs Improperly Narrow The Scope And Content Of The Prior Art.

Focusing on the inventors' testimony, particularly the problems they sought to solve, Plaintiffs improperly attempt to restrict the prior art available to the skilled artisan. *See, e.g.*, D.I. 251 (08-330-SLR) at 13 (distinguishing Halpern on the basis that it "does not contemplate or address any of the challenges that Dr. Zhang recognized . . . ."); *see also id.* at 49-52. "One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." *KSR*, 550 U.S. at 419-20. However,

> [t]he actual inventor's skill is irrelevant to the inquiry . . . . The statutory emphasis is on a person of *ordinary* skill . . . . [O]ne should not go about determining obviousness under § 103 by inquiring into what *patentees* (i.e., inventors) would have known or would likely have done, faced with the revelations of the references.

Standard Oil v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985) (emphasis in original). Here, a skilled artisan would be directed to the prior art references Defendants have identified. *See, e.g.*, D.I. 245 (08-330-SLR) at 15-19, 39-41.

C. Plaintiffs Apply An Improperly Narrow Analysis Regarding The Motivation To Combine.

Defendants have shown that a skilled artisan would have had been sufficiently motivated to combine the prior art references to reach the inventions of the asserted claims with a reasonable expectation of success. *Id.* at 21-23, 41-44. Defendants have applied the common sense, flexible analysis endorsed by the Supreme Court to demonstrate a motivation to combine. *Id.*; *KSR*, 550 U.S. at 415, 417-18, 421, 424. Plaintiffs, in contrast, focus on the problems faced by the inventors. *See* D.I. 251 (08-330-SLR) at 16-17, 19-22, 54. But *KSR* highlighted the impropriety of this approach. 550 U.S. at 418-20.

Plaintiffs' allegation that a person of ordinary skill in the art would have no reasonable expectation of success in combining the prior art references, D.I. 251 (08-330-SLR) at 19-21, 49-50, is similarly infirm for its reliance on subjective inventor testimony. *Compare id.* at 20-21 (focusing on Dr. Zhang's problem and solution) *and id.* at 49-50 (focusing on Dr. Khankari's problem and solution) *with Life Techs.*, 224 F.3d at 1326 ("Reasonable expectation of success is assessed from the perspective of the person of ordinary skill in the art.").

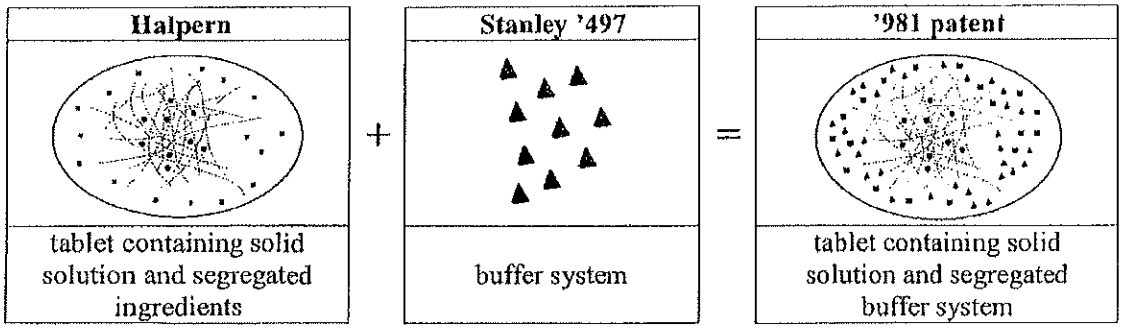
Further, Defendants' evidence and analyses of motivation to combine avoided the very hindsight bias that Plaintiffs accuse Defendants of adopting. D.I. 251 (08-330-SLR) at 2, 26-27, 41, 50, 52-53; D.I. 245 (08-330-SLR) at 21-23, 41-44. As the Federal Circuit stated: "To preclude hindsight in this analysis, this court flexibly seeks evidence from before the time of the invention in the form of some teaching, suggestion, or even mere motivation (conceivably found within the knowledge of an ordinarily skilled artisan) to make the variation or combination." *Rolls-Royce, PLC v. United Techs. Corp.*, 603 F.3d 1325, 1338 (Fed. Cir. 2010) (citations omitted).

Accordingly, Defendants have shown by clear and convincing evidence, using the proper analytical framework, that all of the asserted claims are obvious.

II. THE ASSERTED CLAIMS OF THE '981 PATENT ARE OBVIOUS.

To invalidate the asserted claims of the '981 patent, the Court need only answer two questions. First, whether Halpern, which discloses a tablet containing a solid solution and segregated ingredients, combined with Stanley '497, which discloses a buffer system, make obvious claims that recite a "solid solution" with a segregated "buffer system," as depicted below in Figure 1:

FIGURE 1



See Tr. 1013:23-1014:23, 1017:1-1018:23, 1025:6-20, 1029:22-1030:8, 1031:5-1034:18, 1043:3-14 (Flanagan direct); Tr. 1446:9-17 (Byrn direct); DTX-26, col. 1, ll. 20-21, col. 2, ll. 51-63; DTX-55, col. 6, ll. 36-51. And second, whether a skilled artisan would have been motivated to combine Halpern, which teaches that solid solutions improve oral transmucosal formulations by improving drug solubility, with Stanley '497, which teaches that buffer systems improve the absorption of drugs across the oral mucosa.

Defendants have presented clear and convincing evidence demonstrating that the answer to both questions is "yes." Accordingly, asserted claims 3, 5, 32, and 54 are obvious.

A. The Prior Art Discloses All Of The Claim Limitations.

Cephalon does not dispute that Stanley '497 discloses a "buffer system." *Id.* at 23. Cephalon wrongly argues, however, that the prior art does not disclose the "solid solution" and "micro-environment" claim limitations, or ingredients segregated from the "solid solution." *Id.* at 11. As demonstrated in Defendants' Opening Brief and below, the prior art cited by Defendants discloses all of the claim limitations. D.I. 245 (08-330-SLR) at 15-28.

1. Stanley '953 And Oralet® Disclose "solid solutions" Containing Fentanyl Citrate.

Cephalon argues that Stanley '953 and Oralet® do not disclose a "solid solution." D.I. 251 (08-330-SLR) at 11, 15-18. But Example 1 of the '981 patent and Example 1 of Stanley '953 are nearly identical, and if one creates a "solid solution," then the other must as well. JTX-5, col. 11, l. 66-col. 12, l. 7; DTX-37, col. 5, ll. 23-57; Tr. 1010:6-1012:24 (Flanagan direct); Tr. 710:23-711:10 (Byrn direct). The '981 patent states that sucrose, dextrose, and fructose—co-dissolved with fentanyl in Example 1 of Stanley '953—are dissolution agents. Tr. 547:8-23, 549:16-24 (Zhang cross); JTX-5, col. 7, ll. 21, 34; DTX-37, col. 5, ll. 23-57. The '981 patent also references fentanyl, the same drug that is used in Example 1 of Stanley '953, as a drug that can combine to form "solid solutions." JTX-5, col. 9, l. 64; DTX-37, col. 5, ll. 23-57. Example 1 of the '981 patent indicates that when a drug and dissolution agent are co-dissolved and then cooled, a "solid solution" forms. JTX-5, col. 11, l. 66-col. 12, l. 7; Tr. 543:14-23 (Zhang cross). Therefore, the process in Example 1 of Stanley '953 must also form a "solid solution."

Additionally, as Cephalon recognized, Oralet® is the prior art commercial embodiment of Stanley '953 and would have contained a "solid solution" if the process described in Stanley '953 created one. D.I. 251 (08-330-SLR) at 9; Tr. 1012:25-1013:21 (Flanagan direct); DTX-19 at CEP-FEN00954974; Tr. 1456:1-5 (Byrn direct).

2. Halpern Discloses A "solid solution."

Even though Halpern uses the term "solid solution," Cephalon tries to dismiss Halpern as a relevant reference relating to "solid solutions" because that term allegedly was not explicitly defined in Halpern and allegedly was not in the lexicon of the art when Halpern was published in 1955. D.I. 251 (08-330-SLR) at 11-13; DTX-26, col. 1, ll. 20-21. Cephalon makes this argument despite its expert's admissions that Halpern describes a manufacturing process that is the same as an example in the '981 patent, which inventor Dr. Zhang testified results in a "solid solution."

Halpern discloses the same "solid solution" as the '981 patent because both patents disclose the same manufacturing process. *E.g.*, DTX-26, col. 13, ll. 17-22; JTX-5, col. 2, ll. 7-14; Tr. 1033:20-1035:12 (Flanagan direct). Dr. Byrn admitted that the PEG-and-drug co-melts in Examples I-V of Halpern are "just like" Example 2 of the '981 patent, and Dr. Zhang testified that Example 2 of the '981 patent creates a "solid solution." Tr. 1466:1-18 (Byrn cross); Tr. 532:17-533:15, 535:14-23, 548:21-549:15 (Zhang cross). Thus, the only reasonable conclusion is that both Halpern and the '981 patent disclose a "solid solution."

Furthermore, the relevant legal inquiry is whether, in 1999, a skilled artisan would have understood that Halpern discloses a "solid solution." *See In re Andros*, No. 91-1475, 1993 WL 16069, at *2 (Fed. Cir. Jan. 28, 1993). Dr. Byrn admitted that "solid solutions" were known in the art since at least the "early 1970s,"[1] and Dr. Zhang admitted that Cephalon did not invent "solid solutions." Tr. 1474:21-1475:5 (Byrn cross); Tr. 542:4-7, 543:4-13 (Zhang cross). Thus,

[1] Plaintiffs' Exhibit 1 to their Responsive Brief contains selected deposition testimony of Dr. Byrn. D.I. 251 (08-330-SLR) at 13 n.3 (referencing Ex. 1). None of this deposition testimony was read into the record, or otherwise admitted at trial under the Federal Rules of Evidence. Plaintiffs purportedly include Exhibit 1 to rebut a motion to strike related trial testimony of Dr. Byrn. *Id.* But Defendants have made no such motion. Accordingly, Plaintiffs' submission of Exhibit 1 violates the Federal Rules and this Court's Briefing Guidelines in Patent Cases ("Briefing Guidelines"). It should be disregarded.

a skilled artisan in 1999 would have understood the "solid solution" disclosed in Halpern to be the same "solid solution" claimed in the '981 patent. DTX-26, col. 1, ll. 20-21.

3. Halpern Discloses A "solid solution micro-environment" And Ingredients Segregated From The "micro-environment."

a. The '981 Patent's Claims, As Construed By Both Parties, Define A "micro-environment" As A "solid solution" With A Segregated Ingredient.

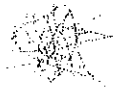
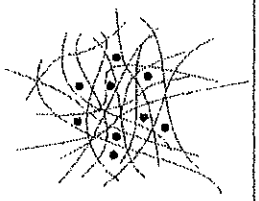
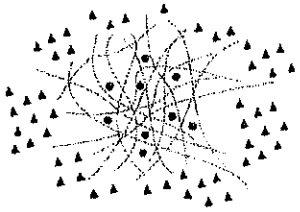
Cephalon argues that the prior art does not disclose the "micro-environment" and "physical barrier"[2] limitations, as construed by both parties. *E.g.*, D.I. 251 (08-330-SLR) at 12, 14. In doing so, Cephalon misapplies the law and expands the scope of the asserted claims by impermissibly comparing the prior art to problems Anesta and Dr. Zhang encountered in formulating etomidate, rather than comparing the prior art to the claims. *Id.* at 7-8, 10-15; *see In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993) ("It is axiomatic that the claims define the invention which an applicant believes is patentable.").

As the parties agree, the "micro-environment" and "physical barrier" limitations require only that an ingredient (here, a "buffer system") is located outside, i.e., "segregated" from, the "solid solution." D.I. 187 (08-330-SLR) at 3. The '981 patent teaches how this segregation occurs. Example 2 forms a "solid solution micro-environment" and "physical barrier" through a partial co-melt process. Tr. 1017:9-1018:6, 1025:6-1026:8, 1034:10-18, 1034:19-1036:2 (Flanagan direct); Tr. 532:17-535:5 (Zhang cross); Tr. 747:3-9, 1441:8-23, 1444:17-1445:14 (Byrn direct). The drug and dissolution agent are melted together to form a liquid solution. *Id.* When the liquid solution cools and solidifies, it forms a "solid solution." *Id.* An ingredient is

[2] The parties did not construe the term "physical barrier," but the parties agree that it means the same thing as the term "micro-environment." *See* Tr. 1017:12-1018:6 (Flanagan direct); Tr. 747:3-9 (Byrn direct); Tr. 532:17-535:5 (Zhang cross).

"segregated" from (i.e., outside of) the "solid solution" if the ingredient is dry mixed with the "solid solution," as demonstrated below in Figure 2. *Id.*

FIGURE 2

Drug: 	The drug and dissolution agent are melted together to form a **liquid** solution	When the co-melt is cooled, the ingredients in the **liquid** solution form a **solid** solution	When a dry ingredient is added to the **solid** solution, the dissolution agent "segregates" that ingredient from the solid solution and the drug
Dissolution agent 			
Dry ingredient 			

Id. The parties agreed with this interpretation of "micro-environment" and "segregation." *Id.*; Tr. 710:23-711:10, 712:21-713:4 (Bryn direct); Tr. 532:25-535:4 (Zhang cross).

b. Halpern Discloses A "micro-environment."

In Example I, Halpern discloses creating a tablet by melting PEG together with a drug to form a liquid solution, cooling that liquid solution to form a "solid solution," pulverizing and granulating the "solid solution," and pressing the granulate into tablets. DTX-26, col. 2, ll. 7-12; Tr. 1031:5-1034:18 (Flanagan direct). Examples II-IV are variations of Example I that also form a "solid solution" using PEG. DTX-26, col. 2, ll. 20-50; Tr. 1029:22-1030:8 (Flanagan direct). Notably, each example concludes by stating that the compositions were compressed into tablets in the same way as "Example I." DTX-26, col. 2, ll. 20-50.

Example V is the last variation of Example I. DTX-26, col. 2, ll. 52-63; Tr. 1031:5-1034:18 (Flanagan direct). In this example, the "solid solution" of PEG and a drug is again made and "[t]o the compositions thus formed, inert ingredients . . . are added." DTX-26, col. 2, ll. 52-54; Tr. 1029:1-21 (Flanagan direct). Read in context with Examples I-IV, a skilled artisan

would understand the words "compositions thus formed" in Example V to mean that PEG and the drug digitoxin were cooled to make the "solid solution" composition (as they were in Examples I-IV) before the "inert ingredients" were added. *Id.*; Tr. 1029:22-1030:8 (Flanagan direct).

Dr. Byrn admitted that Halpern's Example V is "just like" Example 2 of the '981 patent. Tr. 1466:1-24 (Byrn cross); Tr. 1034:19-1036:2 (Flanagan direct). Both create a liquid solution by co-melting PEG with a drug. Tr. 1031:5-1032:4, 1035:14-16 (Flanagan direct); DTX-26, col. 2, ll. 52-54; JTX-5, col. 13, ll. 17-20. Both allow the solution to cool, forming a "solid solution." DTX-26, col. 2, ll. 12; JTX-5, col. 13, ll. 20; Tr. 1029:22-1030:8, 1035:14-16 (Flanagan direct). Both then add dry ingredients to the "solid solution." *Id.*; DTX-26, col. 2, ll. 54-61; JTX-5, col. 13, ll. 20-22; Tr. 1035:24-1036:2 (Flanagan direct). This is the same process illustrated in Figure 2, above. And Dr. Zhang admitted that this process creates a "micro-environment" in the '981 patent. Tr. 532:25-535:4 (Zhang cross).

Further, the nature of the "inert ingredients" listed in Halpern's Example V would teach a skilled artisan to add them outside of the "solid solution," after it had cooled. The ingredients listed include magnesium stearate and talc, which are usually added at the very last step in tablet manufacture (in the case of Example V, after cooling) to lubricate the tablet press die wall. Tr. 1029:22-1031:2 (Flanagan direct). If talc and magnesium stearate were added to the liquid solution, they would form part of the "solid solution" and the PEG barrier would prevent the lubricant from contacting the die wall and lubricating the die. *Id.* Dr. Byrn recognized this and admitted that "a formulator, making a tablet per the teaching of Halpern, may elect to add a lubricant just immediately before pressing a tablet in order to provide lubrication for the die," and that this would segregate the lubricant from the "solid solution." D.I. 251 (08-330-SLR) at

14; Tr. 1446:9-17 (Bryn direct). Cephalon cannot reasonably dispute that Halpern teaches a tablet containing a "solid solution" with segregated ingredients.

When testifying on infringement, Dr. Byrn alleged that the ANDA products meet the "micro-environment" and "physical barrier" limitations because Watson Laboratories mixes potassium bicarbonate and magnesium stearate with the dried granules allegedly containing a "solid solution" of fentanyl citrate and sodium starch glycolate. Tr. 737:3-20, 754:7-756:13 (Byrn direct); *see* D.I. 244 (08-330-SLR) at 54, 57. If adding an ingredient outside of the "solid solution" meets the "micro-environment" and "physical barrier" limitations for infringement purposes, then Halpern necessarily must meet those limitations for invalidity purposes. *Cf. Lewmar Marine, Inc. v. Barient, Inc.*, 827 F.2d 744, 747 (Fed. Cir. 1987) ("That which would literally infringe if later in time anticipates if earlier than the date of invention").

Moreover, Halpern teaches a tablet containing a "solid solution" and segregated "buffer system," as Dr. Byrn defines that term[3]:

> Q. Okay. And so Example 5 [of Halpern] teaches making a co-melt of PEG and a drug . . . and to the composition then formed, adding a variety of things, including sodium bicarbonate, which, by your own words, is both a buffer and a pH-adjusting substance. Correct, Doctor?
>
> A. It -- it teaches that. . . .

Tr. 1470:12-19 (Byrn cross). A skilled artisan also would have understood that buffers may degrade drugs and would have understood that sodium bicarbonate should be added outside of

[3] Defendants have explained that a carbonate source, such as sodium bicarbonate or potassium bicarbonate, is not a "buffer system" because it is not a conjugate acid/base pair that resists both increases and decreases in pH. D.I. 253 (08-330-SLR) at 36-38. But Dr. Byrn took the position on infringement that an amphoteric substance like potassium bicarbonate or sodium bicarbonate alone would be a "buffer system." *Id.*; Tr. 740:14-741:14 (Byrn direct). Thus, Dr. Byrn stated that the sodium bicarbonate in Example V of Halpern is also a "buffer system." Tr. 1470:12-19 (Byrn cross).

the "solid solution." Tr. 1471:8-1472:12 (Byrn cross). Therefore, Halpern discloses a tablet containing a "solid solution" with—as defined by Dr. Byrn—a segregated "buffer."

Additionally, Halpern states that it is "convenient to use the polyoxyethylene glycol [PEG] alone as the vehicle for the active ingredient," meaning that any other ingredients are not in the "solid solution" granules—and that "[t]he invention includes also tablets, in which other ingredients . . . are present . . . ." DTX-26, col. 4, ll. 5-14. This would teach a skilled artisan that only PEG and a drug should be placed in "solid solution" to form the "vehicle," and that any other ingredients should be added outside of the "solid solution" to form the "tablet." *Id.*

c. Cephalon Improperly Reads Unclaimed Subject Matter Into The Claims When Arguing That Halpern Does Not Disclose The "physical barrier" And "micro-environment" Limitations.

Cephalon argues that Halpern does not disclose a "solid solution micro-environment" because "Halpern does not teach . . . [how] to control and optimize dissolution, dissolution rate, and absorption . . . [or] any of the challenges that Dr. Zhang recognized, including . . . the difference between dissolution and solubility, of controlling dissolution, [or] of improving dissolution and absorption . . . ." D.I. 251 (08-330-SLR) at 12-13. As previously discussed, these arguments are legally irrelevant because none of these concepts appears in the claims or the limitations as construed. *See supra* § I; *see also* D.I. 245 (08-330-SLR) at 30-31. Under the law, it is the claims that define the invention. *In re Van Geuns*, 988 F.2d at 1184.

4. Stanley '497 Discloses "buffer systems" For Increasing Absorption Of Ionizable Drugs.

The parties do not dispute that Stanley '497 discloses solid dosage forms containing "buffer systems" to increase absorption of a drug across the oral mucosa. Tr. 1013:23-1014:23 (Flanagan direct); DTX-55, col. 6, ll. 36-51. Therefore, the prior art discloses all of the limitations of the asserted claims of the '981 patent.

B. A Skilled Artisan Would Have Been Motivated To Combine Halpern And Stanley '497 In The Manner Claimed.

A skilled artisan must be motivated to combine prior art references in the manner claimed. The Supreme Court has instructed courts to take an "expansive and flexible approach" and to use common sense when considering the motivation to combine references. *KSR*, at 550 U.S. at 415; *see supra* § I.C. Following this approach, Defendants have properly demonstrated a motivation to combine the prior art references.

1. Halpern And Stanley '497 Disclose Solutions To Problems In Oral Transmucosal Delivery.

A skilled artisan would have been motivated to combine Halpern and Stanley '497 because they solved problems in oral transmucosal drug delivery. *See* D.I. 245 (08-330-SLR) at 21-23; Tr. 1017:1-7 (Flanagan direct). Cephalon identified three challenges in formulating oral transmucosal dosage forms: (1) a small volume of saliva to dissolve the drug in the mouth; (2) a short period of time for the drug to dissolve in the mouth before the patient swallows it; and (3) poor absorption of the drug across the oral mucosa. Tr. 477:19-478:22 (Zhang direct); Tr. 1423:8-20, 22-25, 1425:22-1426:2, 1426:23-1427:8-14 (Byrn direct).

The first two problems relate to the drug's solubility. As Dr. Byrn and Cephalon admit, Halpern recognized the solubility problem and taught that "solid solutions" would solve that problem. D.I. 251 (08-330-SLR) at 21; Tr. 1006:18-1009:8 (Flanagan direct); Tr. 1423:8-20, 22-25, 1430:15-22, 1433:12-20, 1464:14-1465:10 (Byrn direct); DTX-26, col. 1, ll. 15-22. Regarding the third problem, Stanley '497 disclosed that a "buffer system" enhanced absorption across the oral mucosa by converting an ionizable drug to its unionized state. Tr. 1013:23-1014:23 (Flanagan direct); DTX-55, col. 6, ll. 36-51 (buffer systems increase absorption), col. 8, l. 57 (fentanyl). The importance of pH and the use of "buffer systems" to improve absorption of ionizable drugs was widely known. JTX-5, col. 4, ll. 58-63; *see* Tr. 1200:18-1201:4 (Mumper

direct) (explaining that Streisand et al., DTX-273 at 759, discloses a pH-adjusted solution of fentanyl citrate that improved the absorption of fentanyl by placing it in its unionized form).

The Federal Circuit has found a motivation to combine references where the references taught features that would be desirable together. *See In re Kahn*, 441 F.3d 977, 983 (Fed. Cir. 2006). A skilled artisan would have been motivated to create a tablet with both a "solid solution" and a "buffer" to increase both solubility and absorption by combining Halpern and Stanley '497.

2. A Skilled Artisan Would Have Been Motivated To Add The "buffer system" Disclosed In Stanley '497 Outside Of (And Segregated from) The "solid solution" Disclosed In Halpern.

A skilled artisan would have been motivated to add the "buffer system" disclosed in Stanley '497 outside of the "solid solution" disclosed in Halpern, thereby segregating it. Where "there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *KSR*, 550 U.S. at 421. Here, there are only two ways to add a "buffer" to a tablet containing a "solid solution"—the "buffer" can either go inside or outside of the "solid solution."

The skilled artisan had good reasons to add the "buffer" outside of the "solid solution." First, a skilled artisan would want to keep the formulation as simple as possible and adding the "buffer" to the "solid solution" is more complicated than adding it to the dry tablet. Tr. 1028:15-25 (Flanagan direct). Second, a person having ordinary skill in the art would have realized that adding a "buffer" to the co-melt of PEG and digitoxin could cause the "buffer" to react with the drug and he or she would not have wanted to mix two potentially reactive compounds at the molecular level. Tr. 1471:8-1472:12 (Byrn cross). Third, Halpern taught making the "solid solution" of the drug and PEG first, and then adding to that composition any additional

ingredients such as the "buffer." *See supra* § II.A.3.b; Tr. 1470:12-19 (Byrn cross).

3. Cephalon's Argument That A Skilled Artisan Would Not Have Been Motivated To Combine Halpern And Stanley '497 Because Of Specific Problems That Dr. Zhang Faced Is Legally Incorrect.

Cephalon argues that a person of ordinary skill in the art would not have combined Halpern and Stanley '497 because the prior art addresses different problems than the '981 patent's inventor allegedly encountered. D.I. 251 (08-330-SLR) at 20-21. The Federal Circuit has rejected this reasoning numerous times. *See, e.g., In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992) ("As long as some motivation or suggestion to combine the references is provided by the prior art taken as a whole, the law does not require that the references be combined for the reasons contemplated by the inventor.").

Further, Cephalon again ignores the '981 patent's claim terms and constructions. Instead of comparing the prior art to the claims, Cephalon compares the prior art to Dr. Zhang's problems with etomidate. D.I. 251 (08-330-SLR) at 20, 22. Cephalon ignores that the claims that define the invention, not the problems that the inventors faced. This renders Cephalon's argument irrelevant. *KSR*, 550 U.S. at 418; *see supra* § I.

4. The Prior Art Does Not Teach Away.

Cephalon argues that Stanley '497 teaches away from the '981 patent's segregated dosage forms and "micro-environments." D.I. 251 (08-330-SLR) at 12, 22. Cephalon discusses geometric dilution, but points to nothing in Stanley '497 that suggests that "buffers" could not be combined with "solid solutions." *Id.* at 23-25. A reference does not teach away if it expresses a preference but does not "criticize, discredit, or otherwise discourage" the invention claimed. *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Further, Stanley '497 discusses geometric dilution to thoroughly mix dry powders specifically where using liquids for mixing was not appropriate. DTX-55, col. 8, ll. 48-51. That is, Stanley '497 teaches a method of mixing under

certain conditions for a specific purpose; it does not state that this is the only way of mixing, or that a "buffer" cannot be used without this method of mixing.

Accordingly, Defendants have met their evidentiary burden of demonstrating by clear and convincing evidence a *prima facie* case of obviousness. The asserted claims of the '981 patent are therefore invalid.[4]

C. Cephalon Has Not Met Its Burden Of Presenting Evidence Of Secondary Indicia Of Nonobviousness Sufficient To Rebut Defendants' *Prima Facie* Case Of Obviousness Of The '981 Patent.

Cephalon has the burden of introducing evidence of secondary indicia of nonobviousness to overcome Defendants' *prima facie* case of obviousness. *See In re Huang* 100 F.3d 135, 139 (Fed. Cir. 1996). Evidence of secondary indicia must be objective. *See Demaco Corp. v. F. Von Langsdordff Licensing Ltd.*, 851 F.2d 1387, 1391-92 (Fed. Cir. 1988). Although the burden here is on Cephalon, it is Defendants who have introduced strong, objective evidence that secondary indicia of nonobviousness are *not* present in this case. *See* D.I. 245 (08-330-SLR) at 29-31, 51-57. Cephalon, in contrast, improperly relies on unsupported, irrelevant, and conclusory testimony by its own fact and expert witnesses. D.I. 251 (08-330-SLR) at 27-29, 54-57.

Cephalon argues that there was a "failure of others" to develop the invention claimed in the '981 patent because other scientists at Dr. Zhang's own company allegedly had worked on

[4] Additionally, claims 5 and 32 have claim dependency defects and fail to comply with 35 U.S.C. § 112, ¶ 4. D.I. 245 (08-330-SLR) at 8 n.1. Plaintiffs knew of these defects and opted not to correct them before the U.S. Patent and Trademark Office or this Court. The defects on the face of the patent claims are not disputed, and there were no disputed facts concerning these defects at trial. Although Cephalon argues that Defendants have waived their right to contest validity on this basis, D.I. 251 (08-330-SLR) at 29-31, Cephalon does not distinguish *Pfizer, Inc. v. Ranbaxy, Laboratories Ltd.*, 457 F.3d 1284 (Fed. Cir. 2006), under which this Court should hold, as an additional ground, that claims 5 and 32 are invalid. *See* D.I. 245 (08-330-SLR) at 31-32 (citing *Pfizer*, 457 F.3d at 1291-92).

related technology for "two or three years" before he became involved.[5] *Id.* at 27-29. Even if true, this falls far short of the standards for "failure of others" set forth in the very cases cited by Cephalon. *Id.* These cases did not hold that the efforts by the patentees or other scientists at the patentees' own companies were sufficient evidence of nonobviousness. Instead, these cases held that the claims were not obvious based on efforts to develop the claimed invention far more extensive than those alleged here, and/or other multiple factors. *See Micro Chem., Inc. v. Great Plains Chem. Co.*, 103 F.3d 1538, 1545-47 (Fed. Cir. 1997) (finding of nonobviousness based on no evidence of motivation to combine, no reasonable expectation of success, and long-felt need); *In re Dow Chem. Co.*, 837 F.2d 469, 472-73 (Fed. Cir. 1988) (finding of nonobviousness based on "decades of experimentation" in the industry, "five to six years of research" by the patentees, lack of suggestion in the art, expert skepticism, unexpected results, and long-felt need); *Syntex (U.S.A.) LLC v. Apotex Inc.*, No. C 01-02214, 2006 WL 1530101, at *11-18, *21-28 (N.D. Cal. June 2, 2006) (finding of nonobviousness based on unexpected results, lack of motivation to combine, commercial success, licensing, industry acclaim, and "several years" of efforts by others at the inventors' company). Indeed, Cephalon's own argument that only a very select group of scientists—perhaps only those at Anesta—were even working on this technology severely undercuts Cephalon's "failure of others" argument. D.I. 251 (08-330-SLR) at 29.

The entirety of the evidence presented by Cephalon directed to "unexpected results" is Dr. Byrn's conclusory response to a leading question regarding secondary considerations in which he does not even refer to unexpected results, Tr. 1460:4-12 (Byrn Direct); D.I. 251 (08-

[5] Plaintiffs' Exhibit 2 to their Responsive Brief contains selected pages from the Rebuttal Expert Report of Stephen R. Byrn, Ph.D. D.I. 251 (08-330-SLR) at 28 n.7 (referencing Ex. 2). This Expert Report was not admitted at trial under the Federal Rules of Evidence. Plaintiffs purportedly include Exhibit 2 to rebut a motion to strike related trial testimony of Dr. Byrn. *Id.* But Defendants have made no such motion. Accordingly, Plaintiffs' submission of Exhibit 2 violates the Federal Rules and this Court's Briefing Guidelines. It should be disregarded.

330-SLR) at 28, and the unsupported and conclusory statement of a former Anesta and Cephalon employee that the results of work done by other Anesta scientists—*not* the results of Dr. Zhang's experiments—were "quite . . . unexpected . . . ." D.I. 251 (08-330-SLR) at 27-28; Tr. 559:11-560:2 (Maland designation). Such statements fail to provide any objective evidence of nonobviousness and Plaintiffs do not even cite any supportive case law on this point. D.I. 251 (08-330-SLR) at 26-27.

III. THE ASSERTED CLAIMS OF THE ORANGE BOOK PATENTS ARE INVALID AS ANTICIPATED AND/OR OBVIOUS.

Despite Plaintiffs' arguments to the contrary, (1) Hesnard discloses each and every limitation of asserted claims 1, 2, 8, and 10 of the '604 patent, and (2) all of the asserted claims of the Orange Book patents are *prima facie* obvious.

A. Hesnard Anticipates Asserted Claims 1, 2, 8, And 10 Of The '604 Patent.

Plaintiffs do not refute Defendants' evidence that Hesnard discloses "a solid oral dosage form including a pharmaceutically effective amount of an orally administerable medicament" with "at least one effervescent agent" where one places "said solid oral dosage form in the mouth of a patient so that saliva in said patient's mouth activates said at least one effervescent agent in said tablet." To determine whether Hesnard anticipates claims 1, 2, 8, and 10 of the '604 patent, this Court need only consider whether Hesnard discloses: (1) delivery across the oral mucosa; (2) an effervescent agent "in an amount sufficient to increase absorption;" (3) an "orally administerable medicament [that] is not substantially encompassed by or dispersed in a material that prevents absorption;" and (4) "holding said solid oral dosage." Defendants have presented clear and convincing evidence that Hesnard discloses these limitations, as discussed in their Opening Brief and below. D.I. 245 (08-330-SLR) at 32-60.

1. Plaintiffs' Arguments That Hesnard Does Not Anticipate Claims 1, 2, 8, And 10 Of The '604 Patent Are Legally Incorrect.

a. Plaintiffs' Focus On The General Disclosure Of Hesnard And Subject Matter Not Claimed In The '604 Patent Is Legally Improper.

Plaintiffs argue that Hesnard is not anticipatory because it "focuses primarily, if not exclusively, on gastrointestinal drug absorption," and because it does not discuss a "dynamic pH" effect. D.I. 251 (08-330-SLR) at 31, 34, 36, 37. This argument is legally incorrect. To anticipate, Hesnard need only disclose what is claimed in claims 1, 2, 8 and 10—and it does. *See, e.g., In re Guess*, 347 F. App'x 558, 561 (Fed. Cir. 2009) ("[F]or purposes of anticipation, what is important is what is claimed by the patentee . . . ."); *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1571 (Fed. Cir. 1988) ("And it is claims, not specifications, that are anticipated."). Plaintiffs attempt to obfuscate Defendants' clear and convincing evidence by arguing that Hesnard's objective is not the same as the objective of the '604 patent. D.I. 251 (08-330-SLR) at 32; *see* Tr. 1335:4-18 (Williams direct). But the relevant question is whether Hesnard discloses what is claimed by the '604 patent. *See In re Guess*, 347 F. App'x at 561; *Constant*, 848 F.2d at 1571. And in fact, Hesnard speaks directly to the claims, disclosing "[a] solid delivery form for placing in the oral cavity" where "a compound or mixture of compounds . . . when contacted with the oral cavity, can form microbubbles for keeping the active principle solubilised . . . ." DTX-64 at WLIJ0305939.

Further, Plaintiffs' lengthy argument that a "dynamic pH" effect is not disclosed by Hesnard is not legally relevant and should be disregarded because "dynamic pH" is not claimed, or even discussed, in the '604 patent. *See In re Guess*, 347 F. App'x at 561; *Constant*, 848 F.2d at 1571; *see also In re Gleave*, 560 F.3d 1331, 1336 (Fed. Cir. 2009) (explaining that an anticipatory reference need not disclose more detail than the patent has in its claims).

Plaintiffs also fixate on the number of recitations of "perlingual" treatment that appear in Hesnard in an attempt to demonstrate that Hesnard's disclosure is insufficient for the purposes of anticipation. *See* D.I. 251 (08-330-SLR) at 33-35; DTX-64 at WLIJ0305944, WLIJ0305950. Plaintiffs' arguments fail, for "as long as the reference discloses all of the claim limitations and enables the 'subject matter that falls within the scope of the claims at issue,' the reference anticipates . . . ." *In re Gleave*, 560 F.3d at 1334 (citations omitted). Here, Hesnard discloses all of the claim limitations, and provides a "reasonable amount of guidance" for preparing an oral mucosal dosage form. *Elan Pharms., Inc. v. Mayo Found. Med. Educ. & Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003). Specifically, Hesnard discloses "high viscosity" for "adhere[nce] to the mucous membrane making it possible for the active principle to better diffuse and reach the general circulation." DTX-64 at WLIJ0305950. In fact, the bioadhesive it teaches to generate that viscosity—CMC—is also taught by the '604 patent for the same purpose. JTX-1, col. 4, ll. 21-39. Further, Plaintiffs' argument that perlingual use was only "contemplate[d]" by Hesnard is legally irrelevant because an anticipatory reference need not actually create or reduce to practice the alleged invention of the patent-in-suit. *Elan Pharms.*, 346 F.3d at 1055; D.I. 251 (08-330-SLR) at 33-35.

b. Plaintiffs' Legal Errors Are Fatal To Their Arguments That Hesnard Does Not Disclose The "holding" Limitation.

Plaintiffs' argument that Hesnard does not disclose "holding said solid oral dosage form . . ." is based on at least two legal errors: (1) misapplication of the doctrine of claim differentiation; and (2) improper product-to-product comparison. Regarding claim differentiation, Plaintiffs argue that since the '604 patent's "claim 6 further requires a bioadhesive [this] demonstrates that bioadhesion is not the same as 'holding' . . . ." D.I. 251 (08-330-SLR) at 39. But Plaintiffs' logic fails as a reference that anticipates a dependent claim

necessarily anticipates the related independent claim. *See Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1299-1300, 1309 (Fed. Cir. 2002). Here, the use of a bioadhesive is merely a subset, or a means, to meet this limitation. *See* Tr. 1246:1-8 (Mumper cross). In fact, the use of a bioadhesive in Hesnard, coupled with the disclosure of perlingual administration, is evidence that Hesnard intended that the dosage form be held in the mouth for a period of time. *Id.* That is all that is required by the claims of the '604 patent. The '604 patent discloses bioadhesives to "increase the residence time of the dosage form in the oral cavity." JTX-1, col. 4, ll. 26-31. And claim 6 states that a bioadhesive "increases the contact time between said solid oral dosage form and the oral mucosa," just as Hesnard teaches that the bioadhesive CMC functions based on viscosity. *Id.* at col. 8, ll. 7-13; DTX-64 at WLIJ0305952.

Plaintiffs' product-to-product comparison is also improper. Plaintiffs use Fentora®'s instructions not to suck or chew as evidence that Hesnard does not anticipate the asserted claims because Hesnard discloses sucking and chewing. D.I. 251 (08-330-SLR) at 39. But "[i]t is the presence of the prior art and its relationship to the *claim language* that matters for invalidity." *Zenith Elecs. Corp. v. PDI Commc'n Sys. Inc.*, 522 F.3d 1348, 1363 (Fed. Cir. 2008) (emphasis added). Accordingly, comparing Hesnard to Fentora®'s instructions is improper and irrelevant. The fact that Hesnard uses the words suck and chew and the use of the bioadhesive CMC instead of using the word "holding" is inconsequential. A reference need not use the exact words of a claim to anticipate. *See In re Gleave*, 560 F.3d at 1334.

2. Defendants Have Proven By Clear And Convincing Evidence That Hesnard Anticipates Claims 1, 2, 8, and 10 Of The '604 Patent.

a. Plaintiffs Fail To Rebut Defendants' Evidence That Hesnard Discloses An Effervescent Oral Transmucosal Dosage Form.

Relying on *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008), Plaintiffs argue that Hesnard does not disclose perlingual treatment and the use of microbubbles to

increase absorption. D.I. 251 (08-330-SLR) at 34, 36. But such reliance is improper. In *Net MoneyIN*, 545 F.3d at 1370, the court held that a patent was not anticipated by a prior art reference where the limitations were not "arranged or combined in the same way as in the claim" because the limitations were found in different, discrete examples of the reference. But here, Hesnard discloses the limitations of the '604 patent claims in close proximity to one another and in a continuous description of the invention, indicating that the disclosures are not disparate, but rather relevant to the same subject matter. *See, e.g.*, D.I. 245 (08-330-SLR) at 35-36 (citing, *inter alia*, DTX-64 at WLIJ0305944, WLIJ0305950, WLIJ0305956-57, WLIJ0305959, WLIJ0305961). Moreover, as Plaintiffs point out, Hesnard's discussion of microbubbles is *not* separate from its discussion of perlingual treatment. D.I. 251 (08-330-SLR) at 36. Hesnard discusses gas release in the paragraph *directly following* the discussion of "treatments by perlingual means." Tr. 1207:8-11 (Mumper direct); DTX-64 at WLIJ0305950.

Plaintiffs further argue that Hesnard is not anticipatory because the passages discussing perlingual treatment say "*nothing*" about increased absorption and that Dr. Mumper conceded this. D.I. 251 (08-330-SLR) at 34 (citing Tr. 1238:7-19 (Mumper cross)) (emphasis in original). These arguments are factually inaccurate. Dr. Mumper never made such a concession. Dr. Mumper was only asked about *one* of the passages discussing perlingual treatment and stated that that particular passage did not discuss absorption. Tr. 1238:7-19 (Mumper cross); DTX-64 at WLIJ0305944. Dr. Mumper was never asked, and therefore could never have conceded, that Hesnard—in its entirety—does not discuss perlingual treatment with increased absorption. Moreover, Plaintiffs disregard a passage in Hesnard that states: "A high viscosity also makes it possible to contemplate treatments by *perlingual* means (trinitrite for example). The gel so obtained adheres to the mucous membrane *making it possible for the active principle to better*

diffuse and reach the general circulation." DTX-64 at WLIJ0305950 (emphasis added). Here, the emphasized language speaks directly to the issue of absorption. *Id.*; *see* Tr. 1190:3-12, 1192:1-9 (Mumper direct). Plaintiffs' argument that the passages discussing perlingual treatment say "nothing" about increased absorption is incorrect.[6]

Plaintiffs also argue that Hesnard is not anticipatory because it requires high viscosity for treatment by perlingual means, making effervescence impossible. D.I. 251 (08-330-SLR) at 37, 48. Specifically, Plaintiffs argue and Dr. Williams testified that "one of skill in the art reading Hesnard would understand microbubbles with high viscosity may be and probably would be trapped within the gel structure once it rapidly has been transformed from a solid oral tablet." Tr. 1345:3-6 (Williams direct); D.I. 251 (08-330-SLR) at 37; *see* Tr. 1346:24-1347:3, 1358:14-24 (Williams direct). As evidenced by Dr. Williams' later testimony, however, effervescence and high viscosity created by the bioadhesive CMC—taught in both Hesnard and the Orange Book patents—are not mutually exclusive. When discussing increasing viscosity with CMC, Dr. Williams testified: "[O]ne of skill in the art would understand, he's [Hesnard] trying to confirm that at higher viscosities, effervescent agents are still able to produce microbubbles." Tr. 1352:3-14 (Williams direct); *see* Tr. 1389:3-7 (Williams cross) ("I understand Hesnard['s] results to say that the creation of the microbubble was independent of the presence of CMC.").

This argument also should be afforded no credit because the '604 patent teaches using CMC with effervescence to improve absorption, just as Hesnard does. JTX-1, col. 4, ll. 21-39; *see* Tr. 1191:3-6 (Mumper direct) (testifying that the volume of carbon dioxide release is independent of the use of CMC in Hesnard).

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[6] Notably, Plaintiffs appreciated this disclosure, as this very passage is quoted in Plaintiffs' Responsive Brief. D.I. 251 (08-330-SLR) at 36 (quoting DTX-64 at WLIJ0305950).

b. Hesnard Discloses An "effervescent agent" In "an amount sufficient to increase absorption."

Plaintiffs wrongly assert that Defendants have failed to show that Hesnard discloses an "effervescent agent" in an amount that is greater than necessary to disintegrate a tablet, as required by Defendants' claim construction. D.I. 251 (08-330-SLR) at 37. Dr. Mumper gave four examples where Hesnard discusses production of an amount of gas sufficient to increase absorption that is above the amount needed for disintegration. Tr. 1189:23-1190:16 (Mumper direct). Moreover, Hesnard discloses producing effervescent gas between 1 and 100 cm^3. DTX-64 at WLIJ0305947. This quantity includes the preferred embodiments of the Orange Book patents, which teach producing effervescent gas precisely within this range: 5-30 cm^3. JTX-1, col. 2, ll. 35-40; JTX-3, col. 2, ll. 38-41; Tr. 1190:3-10 (Mumper direct).

c. Hesnard Discloses "wherein said orally administerable medicament is not substantially encompassed by or dispersed in a material that prevents absorption of said medicament across the oral mucosa . . . ."

Plaintiffs argue that Hesnard does not anticipate because it describes the use of CMC to form a high viscosity gel for perlingual treatments that prevents absorption across the oral mucosa. D.I. 251 (08-330-SLR) at 37-38. Plaintiffs offer no explanation or objective evidence to support this assertion. In fact, the Orange Book patents refute Plaintiffs' argument. These patents teach that effervescent agents and bioadhesives (such as CMC) work together to enhance absorption, just as Hesnard teaches. JTX-1, col. 4, ll. 21-39; JTX-3, col. 4, ll. 23-40.

Plaintiffs wrongly rely on the presence of CMC as a bioadhesive in Hesnard to argue that Hesnard discloses a delayed release dosage form, while claim 1 of the '604 patent requires an immediate release. D.I. 251 (08-330-SLR) at 37-38; Tr. 1345:12-1346:10 (Williams direct). But claim 1 of the '604 patent does not recite an immediate release dosage form. JTX-1, col. 7, ll.

12-31. Therefore, whether Hesnard describes a delayed release dosage form is irrelevant. *See In re Guess*, 347 F. App'x at 561; *Constant*, 848 F.2d at 1571.

B. The Asserted Claims Of The Orange Book Patents Are *Prima Facie* Obvious In View Of Stanley '497 In Combination With Hesnard Or Eichman.

Each asserted claim of the Orange Book patents is *prima facie* obvious and Plaintiffs' contrived secondary indicia of nonobviousness fail to rebut Defendants' evidence.

1. Eichman Is Prior Art To The Orange Book Patents.

At trial, Defendants demonstrated that Eichman was prior art under 35 U.S.C. § 102(b) through the testimony of Mr. Richard Reeb, Associate Director for Collection Development and Technical Services at the University of Wisconsin at Madison ("the University"). Tr. 964:6-9 (Reeb direct). To qualify as a printed publication, the publication must have been disseminated or otherwise made accessible to persons interested and ordinarily skilled in the subject matter. *Orion IP, LLC v. Hyundai Motor Am.*, 605 F.3d 967, 974 (Fed. Cir. 2010). Even Plaintiffs pointed out that a reference is publically available if "persons interested and ordinarily skilled in the subject matter" can locate it when "exercising reasonable diligence." D.I. 251 (08-330-SLR) at 43. Defendants met their burden by showing that anyone—anywhere in the United States—had access to Eichman by February of 1996, at the latest. Tr. 966:24-967:10, 970:15-20, 971:19-972:20, 974:16-975:14 (Reeb direct).

Further, Plaintiffs failed to rebut Defendants' evidence of routine business practices at the University, which showed that Eichman was accessible. Tr. 964:6-967:18, 969:25-970:20 (Reeb direct); DTX-432C; *Constant*, 848 F.2d at 1568-69 (Fed. Cir. 1988). Plaintiffs' attempt to discredit Mr. Reeb's testimony by suggesting—with no supporting evidence—that it was possible that Eichman was not physically on the library shelves by January 23, 1996 due to a hypothetical intellectual property hold ("IP hold"). *See* D.I. 251 (08-330-SLR) at 43. But

Plaintiffs' argument fails. Mr. Reeb testified that an IP hold was not only hypothetical, it was unlikely. Tr. 979:17-25, 980:9-19 (Reeb cross). Therefore, Defendants have shown that Eichman was catalogued on January 23, 1996 and accessible to anyone with Internet access. Tr. 964:6-967:18, 969:25-970:20 (Reeb direct); DTX-432C.

2. A Skilled Artisan Would Have Been Motivated To Combine Stanley '497 With Hesnard Or Eichman In The Manner Claimed.

Plaintiffs argue that a skilled artisan would have no reason to combine, nor any expectation of success in combining, Stanley '497 with Hesnard or Eichman. D.I. 251 (08-330-SLR) at 46-52. This argument relies on two central themes: (1) Aungst and Stanley '497 teach away from using effervescence for oral absorption; and (2) the problem Dr. Khankari was trying to solve in the Orange Book patents was a different problem than the one Defendants describe. *Id.* Both arguments are incorrect.

Plaintiffs incorrectly assert that Aungst would caution a skilled artisan against using effervescence for oral transmucosal absorption. *Id.* at 46-47. Aungst merely notes that enhancers that work *primarily* on tight junctions may not affect permeability across the oral mucosa. Tr. 1373:17-1374:1 (Williams direct); DTX-298 at CEP-FEN00004857. It does not suggest that they would impede absorption. Eichman posits numerous advantages to effervescence outside of its effect on tight junctions. For example, Eichman states that "other potential effects of carbon dioxide, i.e. buffering effect, *altering the pH gradient across the mucosa*, etc., may also contribute to the overall enhancement effect . . . ." DTX-434, at CEP-FEN00005023 (emphasis added); *see id.* at CEP-FEN00005025 ("Enhanced drug absorption due to effervescence is a complex phenomenon without a simple explanation."). In addition, Stanley '497 teaches that pH conditions in the mouth affect oral transmucosal absorption. DTX-55, col. 4, ll. 46-58. Even if Aungst noted the possible ineffectiveness of enhancers that work primarily

on tight junctions—which do not exist in the oral mucosa—Eichman and Stanley '497 give other reasons for a person of ordinary skill in the art to turn to effervescence for oral transmucosal administration and have a reasonable expectation of success.

Plaintiffs also contend that there was no motivation to combine because the problem Dr. Khankari faced is not the problem outlined in Defendants' Opening Brief. D.I. 251 (08-330-SLR) at 49. As with the '981 patent, Plaintiffs' subjective analysis, focusing on inventor testimony, is improper. *See KSR*, 550 U.S. at 419-20, *see supra* § I.C.

Plaintiffs also argue that Dr. Mumper's opinion on motivation to combine is conclusory. D.I. 251 (08-330-SLR) at 48. But even in the transcript portion they cite, Dr. Mumper provided support for his conclusion—specifically, that Stanley '497 teaches the need for the rapid onset of fentanyl citrate, the need to alter the pH for unionized drugs, the need to mask a bitter drug like fentanyl citrate, and how effervescence was a well-known taste-masking agent. Tr.1199:16-1200:9 (Mumper direct). Moreover, Plaintiffs neglect to mention that Dr. Mumper testified specifically about the problem at hand, and the state of the art at the time. Tr. 1196:11-1197:10, 1200:10-1204:12 (Mumper direct).

Accordingly, Defendants have introduced clear and convincing evidence that every limitation of the asserted claims is disclosed in the prior art, establishing a *prima facie* case of obviousness.

C. Plaintiffs Have Not Met Their Burden Of Presenting Evidence Of Secondary Indicia Of Nonobviousness Sufficient To Rebut Defendants' *Prima Facie* Case Of Obviousness Of The Orange Book Patents.

Plaintiffs cite no case law[7] or legally meaningful data to support their argument that Fentora® has been a commercial success. Instead, Plaintiffs rely on the biased testimony of one

[7] The only cases Plaintiffs cite concern whether there is a nexus between the commercial success of a product and claimed features, not whether a product is, in fact, a commercial success. D.I. 251 (08-330-SLR) at 55.

of their officers and attorney speculation about possible motives for Defendants and others to seek market approval for a generic version of Fentora®. D.I. 251 (08-330-SLR) at 54-55. Objective data show that Fentora® has not been a commercial success by any relevant measure. D.I. 245 (08-330-SLR) at 51-53. Among other things, Fentora® has achieved only about one-quarter of the sales of its predecessor drug, Actiq®, and only about 0.5% of the patients in the U.S. that fit the Fentora® indication are prescribed Fentora®. *Id.* Moreover, Defendants' economics expert testified that there are a number of reasons a company would want to market a generic version of a drug that is not a "commercial success" under objective, legal standards. Tr. 1506:25-1507:10 (Rausser cross).

Defendants have already addressed Plaintiffs' lack of objective evidence of "surprising results," "long-felt need," and "praise of others." D.I. 245 (08-330-SLR) at 53-57. Plaintiffs notably do not cite a single case in support of their arguments concerning these factors. D.I. 251 (08-330-SLR) at 55-57.

Regarding "surprising results," Plaintiffs rely solely on the self-interested testimony of their own inventor that he experienced a "wow" moment when he received the results of a clinical trial. *Id.* at 55-56; Tr. 145:14-20 (Khankari direct); Tr. 1380:14-20 (Williams direct) (commenting on Dr. Khankari's testimony). Such unsupported, conclusory testimony is not objective evidence of nonobviousness. *See Demaco Corp.*, 851 F.2d at 1391-92.

Regarding "long-felt need," Plaintiffs similarly rely entirely on conclusory testimony of an interested expert[8], unsupported by any documentary evidence whatsoever, that there were concerns with Actiq®. D.I. 251 (08-330-SLR) at 56. Of course, Plaintiffs' "long-felt need"

[8] Plaintiffs' expert, Dr. Fine, is a member of a Cephalon advisory board, was a paid consultant of Cephalon who advocated Fentora® before the FDA, and conceded that he has not actually prescribed Fentora® in more than 2 years. Tr. 1483:1-1484:6 (Fine cross).

argument is belied by the objective evidence that Fentora® has never approached the level of prescriptions achieved by its predecessor drug, Actiq®, and that Fentora® continues to be outsold by Actiq® and its generic versions. Tr. 1494:19-1495:24 (Rausser direct).

Finally, the deficiencies in Plaintiffs' secondary considerations case is starkly demonstrated by their desperate reliance on Dr. Mumper's discussion of Fentora®, among many other drugs including Actiq®, during class lectures as evidence of "praise of others." D.I. 251 (08-330-SLR) at 57. As noted in Defendants' Opening Brief, the information in Dr. Mumper's lecture stemmed from materials prepared by Plaintiffs' scientists as a survey for his students of some recent oral mucosal products. *Id.* at 56-57; Tr. 1328:20-1329:4 (Mumper cross).

IV. THE ORANGE BOOK PATENTS ARE NOT ENABLED UNDER PLAINTIFFS' CONSTRUCTION.

Plaintiffs incorrectly argue that Defendants' evidence of nonenablement was insufficient because Dr. Mumper did not provide an analysis of the *Wands* factors. D.I. 251 (08-330-SLR) at 57. But "it is not necessary that a court review all the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory." *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991); *accord Senju Pharm. Co., Ltd. v. Apotex Inc.*, No. 07-779-SLR, 2010 WL 2380735 at *19 (D. Del. June 14, 2010) (Robinson, J.).

Dr. Mumper's testimony addressed the relevant *Wands* factors, although his opinions were constricted by the limited trial testimony of Dr. Williams regarding his "co-administration theory" and the lack of disclosure in the Orange Book patents. *See* D.I. 245 (08-330-SLR) at 58-60. Dr. Mumper testified that a single-compound "effervescent agent" was not taught in the patent, he had no knowledge of a single-compound "effervescent agent" that could safely be incorporated into a tablet, and a skilled artisan could not practice the co-administration method without undue experimentation. *Id.*; Tr. 1184:12-1186:19 (Mumper direct); *see also* Tr.

1384:15-1385:7 (Williams cross) (admitting that his co-administration theory was not specifically taught in the Orange Book patents and experiments would need to be performed). Accordingly, Dr. Mumper's testimony was sufficient to establish lack of enablement under Plaintiffs' construction.

CONCLUSION

For at least the reasons discussed above and in Defendants' Opening Post-Trial Brief, Defendants have presented clear and convincing evidence that the asserted claims of the '981, '604, and '590 patents are invalid. Accordingly, Defendants respectfully request that this Court enter a judgment of invalidity of each asserted claim of the patents in suit.

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Dated: September 10, 2010

CERTIFICATE OF SERVICE

I hereby certify that on September 10, 2010, I electronically filed the foregoing document with the Clerk of Court using CM/ECF and have sent by electronic mail to the following:

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